SYNTHESIS AND EVALUATION OF PHENOL & ALDEHYDE DERIVATIVES OF SULFONYL CHLORIDE QUINOXALINE

A

SYNOPSIS

SUBMITTED TO JAYOTI VIDYAPEETH WOMEN'S UNIVERSITY

FOR THE AWARD OF DOCTOR OF PHILOSOPHY

IN PHARMACEUTICAL CHEMISTRY

Submitted by

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CERTIFICATE BY THE GUIDE

I hereby declare that this synopsis report **"*Synthesis and Evaluation of Phenol & Aldehyde derivatives of Sulfonyl Chloride Quinoxaline*"** is a bonafide and genuine research work carried out by **Mr. Rakesh Goyal** in partial fulfillment of the requirement for the degree of **"Doctor of Philosophy"** in **Pharmaceutical Chemistry**.

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1. INTRODUCTION

Pharmaceutical chemistry is the chemistry of substances used in medicine. It embraces the main branches of chemistry: radiochemistry, analytical, general, physical and organic chemistry. Pharmaceutical chemistry is concerned more with physically and chemically oriented phases of drug action or availability such as pharmacokinetics, thermodynamics and the assay of drugs in drug system.

Medicinal chemistry is an interdisciplinary science which is more narrowly concerned with the discovery, the development, the isolation, determination of structure and synthesis of compounds (mainly organic) which may be used in medicine it also involves the study of metabolism and mechanism of actions of biologically active compounds at the molecular level and the relationship between structure and biological activity. Medicinal chemistry is also treated under the terms pharmaceutical chemistry, molecular pharmacology, bioorganic chemistry and selective toxicity.[2]

The discipline of the medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic compounds. Inorganic compounds continue to be important in therapy, e.g. trace elements in nutritional therapy, antacids and radiopharmaceuticals, but organic molecules with increasingly specific pharmacological activities are clearly dominant. Development of organic compounds has grown beyond traditional synthetic methods. It includes the exciting new field of biotechnology using the cell's biochemistry to synthesize new compounds. Techniques ranging from DNA and site directed mutagenesis to fusion of cell lines have greatly broadened the possibilities for new entities that treat disease. The pharmacists now dispenses modified human insulin that provide more convenient dosing schedules, cell stimulating factors that have changed the dosing regimen for chemotherapy.

Heterocyclic chemistry To provide an understanding of principles of the medicinal chemistry, it is necessary to consider the physicochemical properties used to develop new pharmacologically active compounds and their mechanism of action, the drug's metabolism including possible biological activities of the metabolites, the importance of stereochemistry in drug design, and the methods used to determine what 'space' a drug occupies.

Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important.

Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings, e.g. most o the members of vitamin B complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, the genetic material, DNA etc. Few of the basics rings of the heterocyclic compounds are listed below.[3]

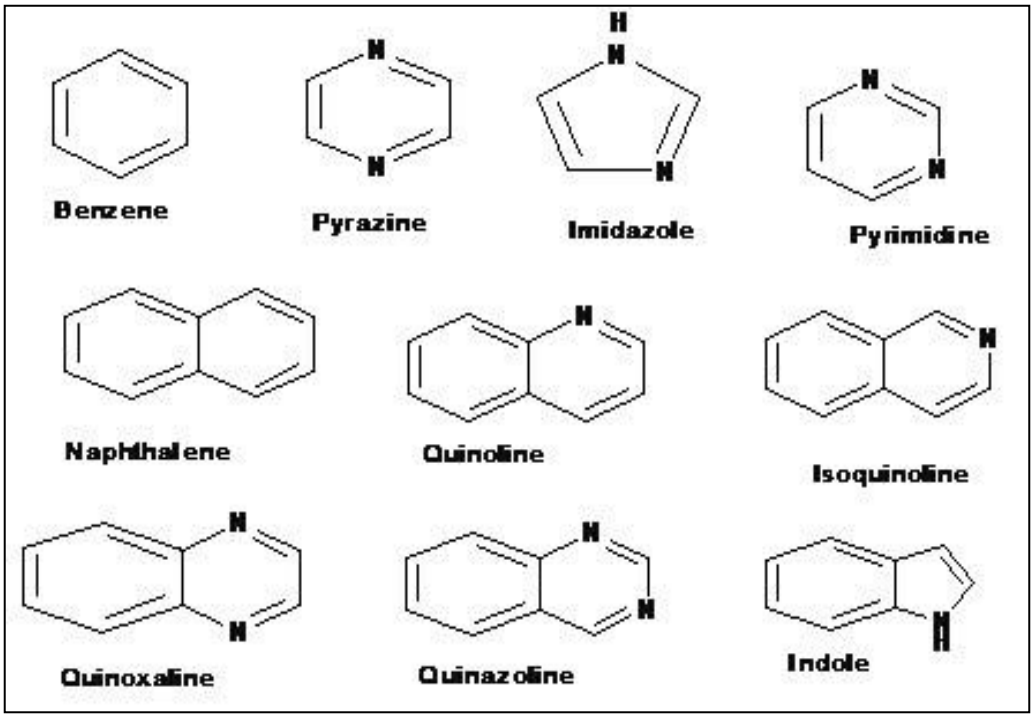
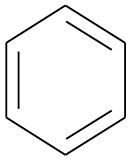
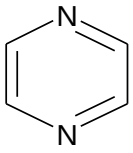


Figure 1: Different heterocyclic rings compound

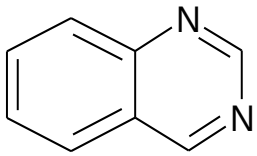
1.1 History



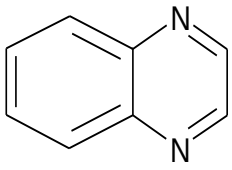
Benzene



Pyrazine



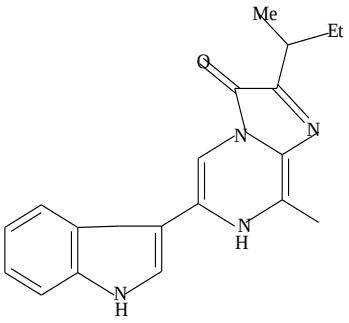
Quinazoline



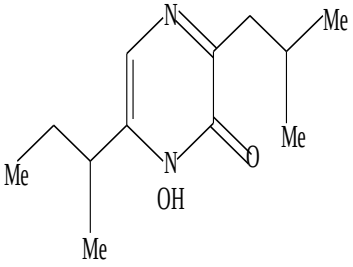
Quinoxaline

Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring & pyrazine ring. Pyrazine are stable, colorless compound which are soluble in water. Unlike pyridine, they are expensive & not readily available & so are seldom used as starting material for synthesis of their derivative. Diazines are fused to benzene ring to form quinoxaline. The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro form in luciferin of several bettles including the fire fly is responsible for the chemiluminescence of this ostracod. Methoxy pyrazine are very important component of aroma of many fruit's and vegetable such as Peas and Capsicum peppers and also of wines.

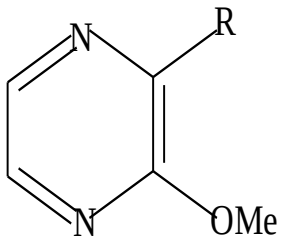
1.1.1 Naturally Occurring Pyrazine & Quinoxaline



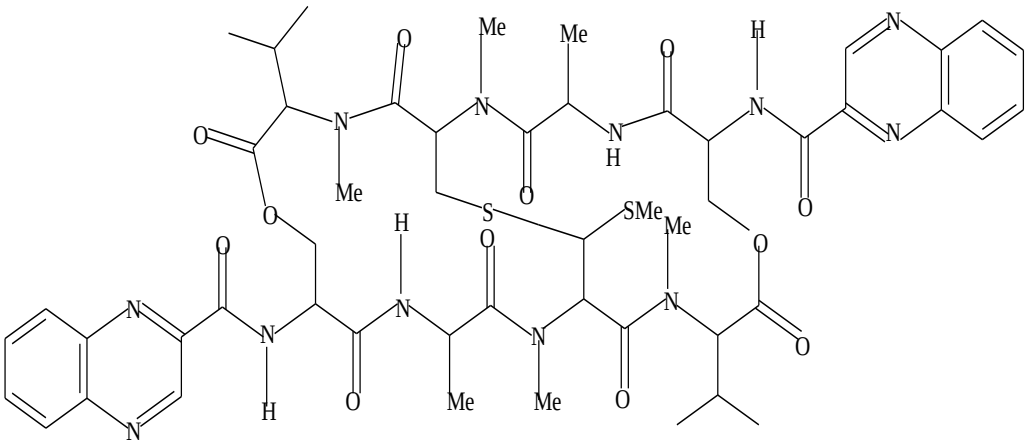
Cyridina Luciferin



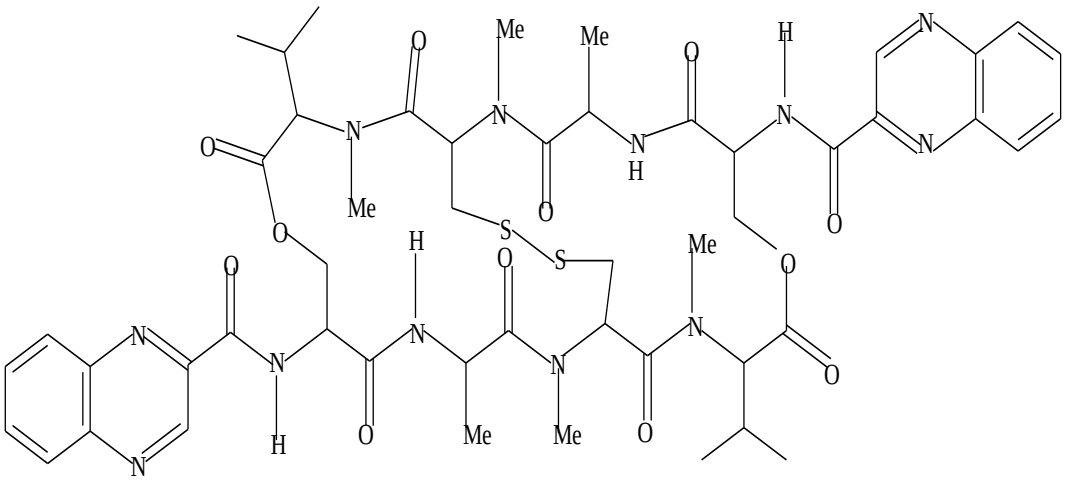
Aspergillic acid



Methoxy Pyrazine (food aroma)

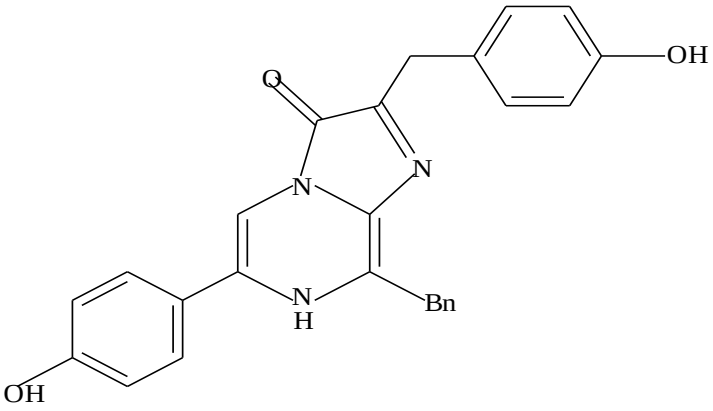


Echinomycin



Triostin A

Cholenterazine: It is synthesized from chloro pyrazine. It is bioluminescent compound from a jellyfish, which potential for use in bioassays.



1.2 Reaction of Quinoxaline

1.2.1 Reaction with electrophilic reagent

1.2.1.1 Addition at nitrogens

1.2.1.1.1 Protonation

The diazines are essentially monobasic substances and considerably weaker as bases than pyridine. In pyrazine mesomeric interaction between the protonated & neutral nitrogen atoms probably destabilizes the cation.N, N'-diprotonation is very easier for pyrazine.[4]

1.2.1.1.2 Oxidation

Pyrazine react with peracid, giving N-Oxides, It can also form N, N- dioxides very easily.

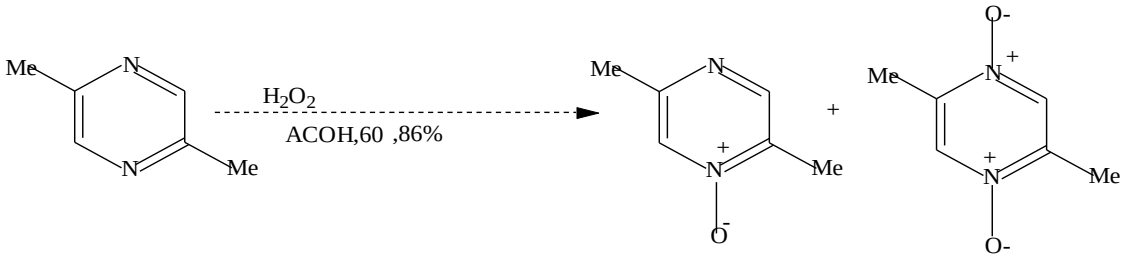


Figure 2: Oxidation of dimethyl pyrazine with hydrogen peroxide.

1.2.1.2 Substitution at carbon:

1.2.1.2.1 Halogenation:

Chlorination of 2-methyl pyrazine occurs under such mild condition that it is almost certain that an addition / elimination sequence is involved, rather than a classical aromatic electrophilic substitution.

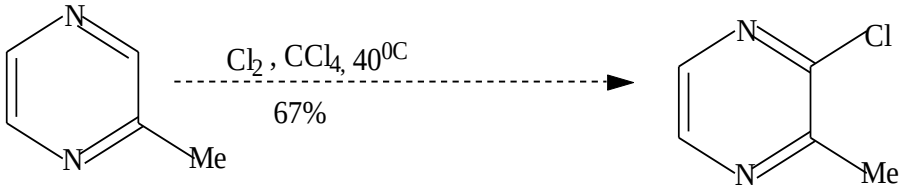


Figure 3: Chlorination of methyl pyrazine in presence of carbon tetrachloride

1.2.2 Reaction with oxidizing agent

The diazines are generally resistant to oxidative attack at ring carbons through alkaline oxidizing agent can bring about degradation via intermediate produced by initial nucleophilic addition. Alkyl substituents fused aromatic rings can be oxidized to carboxylic acid residue leaving the heterocyclic ring untouched.

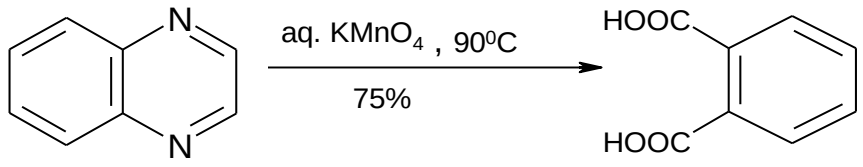


Figure 4: Reaction of quinoxaline with oxidizing agent with potassium permanganate

1.2.3 Reaction with reducing agent

Due to their lower aromaticity, the diazines are more easily reduced than pyridines. Pyrazine and pyridazine can be reduced to hexahydro derivatives with sodium in hot ethanol; under this condition pyridazine has a tendency for subsequent reductive cleavage of the N-N bond. Partial reduction of quaternary salt to dihydro compounds can be achieved with borohydride. 1, 4-Dihydropyrazines have been produced with either silicon62 or amide substitution at the nitrogen atoms, and all the diazines can be reduced to tetra hydro-derivatives with carbamate protection on nitrogen, which aid in stabilization and thus allows isolation.[4]

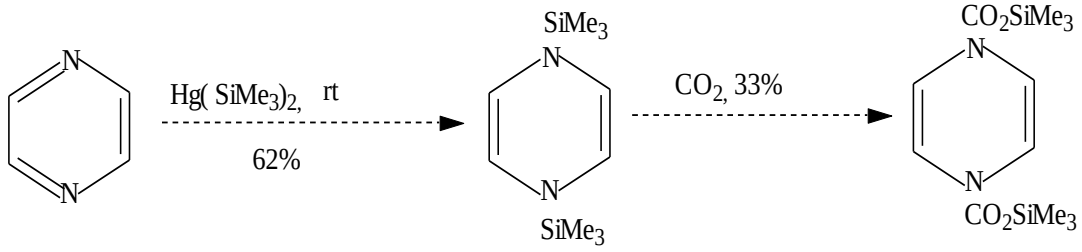


Figure 5: Reaction of pyrazine with reducing agent to give dihydro pyrazine.

1.2.4 Reaction with radical reagents

Radicals add readily to diazines under Minisci condition. Addition to pyrimidine often shows little selectivity, C-2 versus C-4, however a selective Minisci reaction on pyrazines can of course substitute in only one type of position.

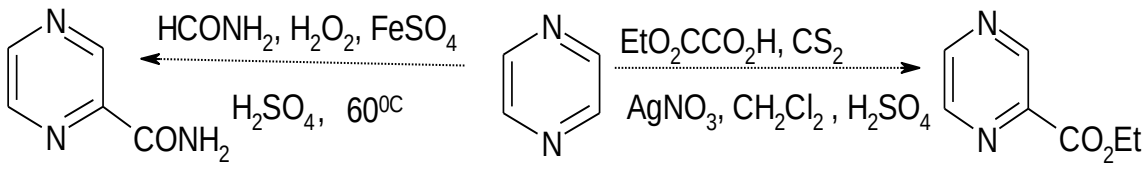


Figure 6: Reaction of pyrazine with radical reagent.

1.2.5 Electrocyclic reaction

Pyrazine having electron withdrawing substituents, undergo Diels-Alder addition with dienophiles. Intermolecular reaction occurs the most readily, these do not even require the presence of activating substituent, immediate product of such process usually loses hydrogen cyanide to generate pyridine product. Singlet oxygen has been added across the 2, 5-position of pyrazine.

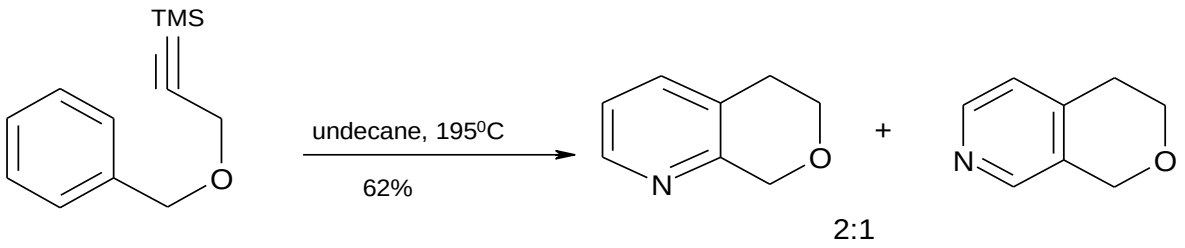


Figure 7: Pyrazine showing Electrocyclic reaction

1.3 Biological activities of quinoxaline

ANTIMICROBIAL:

1.3.1 Antimicrobial Susceptibility Testing

Historically, many infections could be treated successfully based on the clinician's past clinical experience (i.e. empirical therapy). However, this is becoming more the exception than the rule. Resistance has been observed to essentially all of the antimicrobial agents currently approved for use in human and veterinary clinical medicine. This, combined with

the variety of antimicrobial agents currently available, makes the selection of an appropriate agent an increasingly more challenging task. This situation has made clinicians more dependent on data from in vitro antimicrobial susceptibility testing, and highlights the importance of the diagnostic laboratory in clinical practice.

There is a number of antimicrobial susceptibility testing (AST) methods available to determine bacterial susceptibility to antimicrobials. The selection of a method is based on many factors such as practicality, flexibility, automation, cost, reproducibility, accuracy, and individual preference. Standardization and harmonization of AST methodologies, used in epidemiological surveillance of antimicrobial drug resistance, are critical if data are to be compared among national or international surveillance/monitoring programmes of OIE Member Countries.

Selection of antimicrobials for testing and reporting

1. The FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance recommends creating a list of veterinary and human critically important antimicrobials for susceptibility testing and reporting.
2. Antimicrobials in the same class may have similar in-vitro activities against selected bacterial pathogens. In these cases, a representative antimicrobial should be selected that predicts susceptibility to other members of the same class.
3. The number of antimicrobials to be tested should be limited in order to ensure the relevance and practicality of AST.

Selection of antimicrobial susceptibility testing methodology

The selection of an AST methodology may be based on the following factors:[i]

1. Ease of performance,
2. Flexibility,
3. Adaptability to automated or semi-automated systems,
4. Cost,
5. Reproducibility,
6. Reliability,
7. Accuracy,
8. The organisms and the antimicrobials of interest in that particular OIE Member Country,

1.3.2 Antimicrobial susceptibility testing methods

Disk diffusion method

Disk diffusion refers to the diffusion of an antimicrobial agent of a specified concentration from disks, tablets or strips, into the solid culture medium that has been seeded with the selected inoculum isolated in a pure culture. Disk diffusion is based on the determination of an inhibition zone proportional to the bacterial susceptibility to the antimicrobial present in the disk.

The diffusion of the antimicrobial agent into the seeded culture media results in a gradient of the antimicrobial. When the concentration of the antimicrobial becomes so diluted that it can no longer inhibit the growth of the test bacterium, the zone of inhibition is demarcated. The diameter of this zone of inhibition around the antimicrobial disk is related to minimum inhibitory concentration (MIC) for that particular bacterium/antimicrobial combination; the zone of inhibition correlates inversely with the MIC of the test bacterium. Generally, the larger the zone of inhibition, the lower the concentration of antimicrobial required to inhibit the growth of the organisms. However, this depends on the concentration of antibiotic in the disk and its diffusibility.

Advantages

1. Low cost,
2. Ease in modifying test antimicrobial disks when required,
3. Can be used as a screening test against large numbers of isolates,
4. Can identify a subset of isolates for further testing by other methods, such as determination of MICs.

Broth and agar dilution methods

The aim of the broth and agar dilution methods is to determine the lowest concentration of the assayed antimicrobial that inhibits the growth of the bacterium being tested (MIC, usually expressed in mg/ml or mg/liter). However, the MIC does not always represent an absolute value. The ‘true’ MIC is a point between the lowest test concentration that inhibits the growth of the bacterium and the next lower test concentration. Therefore, MIC determinations performed using a dilution series may be considered to have an inherent variation of one dilution. Antimicrobial ranges should encompass both the interpretive criteria (susceptible, intermediate and resistant) for a specific bacterium/antibiotic combination and appropriate

quality control reference organisms. Antimicrobial susceptibility dilution methods appear to be more reproducible and quantitative than agar disk diffusion. However, antibiotics are usually tested in doubling dilutions, which can produce inexact MIC data.

- **Broth dilution**

Broth dilution is a technique in which a suspension of bacterium of a predetermined optimal or appropriate concentration is tested against varying concentrations of an antimicrobial agent (usually serial twofold dilutions) in a liquid medium of predetermined, documented formulation. The broth dilution method can be performed either in tubes containing a minimum volume of 2 ml (macro dilution) or in smaller volumes using micro titration plates (micro dilution).

- **Agar dilution**

Agar dilution involves the incorporation of varying concentrations of antimicrobial agent into an agar medium, usually using serial twofold dilutions, followed by the application of a defined bacterial inoculum to the agar surface of the plate. These results are often considered as the most reliable for the determination of an MIC for the test bacterium/antimicrobial combination.

Advantages:

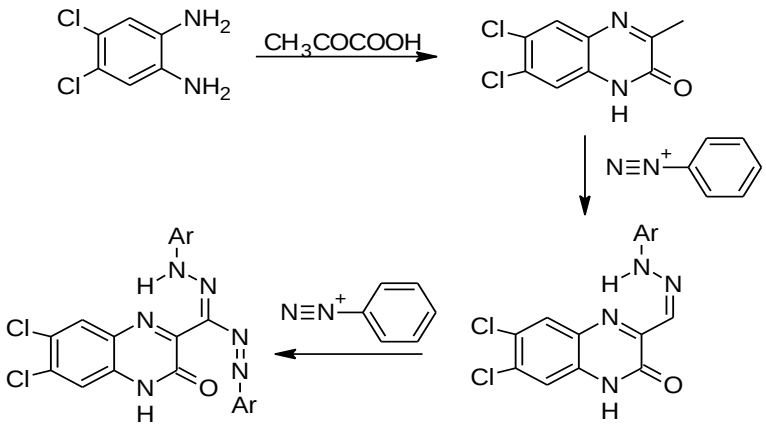
1. The ability to test multiple bacteria, except bacteria that swarm, on the same set of agar plates at the same time,
2. The potential to improve the identification of MIC endpoints and extend the antibiotic concentration range,
3. The possibility to semi-automate the method using an inoculum-replicating apparatus. Commercially produced inoculum replicators are available and these can transfer between 32 and 36 different bacterial inoculam to each agar plate.

Disadvantages

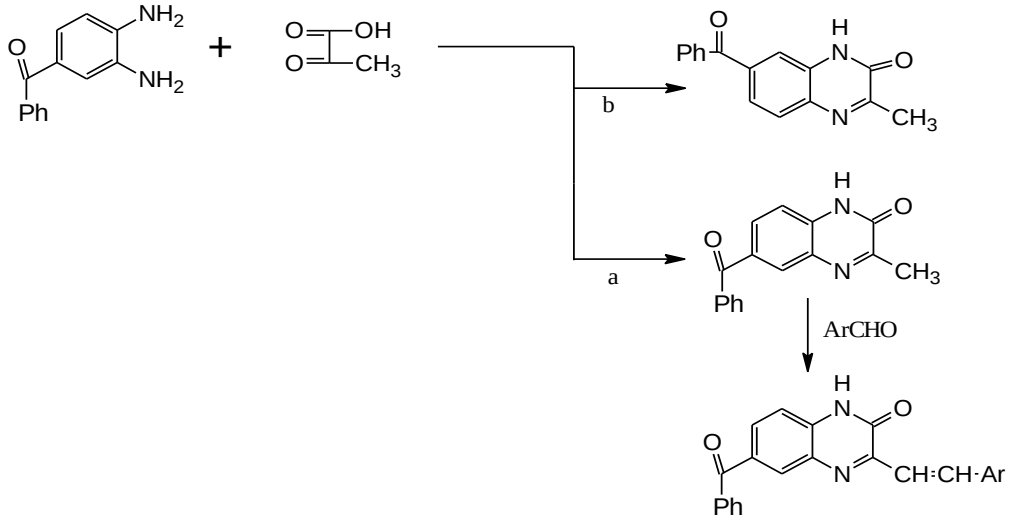
1. If not automated, they are very laborious and require substantial economic and technical resources,
2. Once the plates have been prepared, they normally should be used within a week.
3. The end points are not always easy to read nor are the purity of the inoculum easy to verify.

2. REVIEW OF LITERATURE

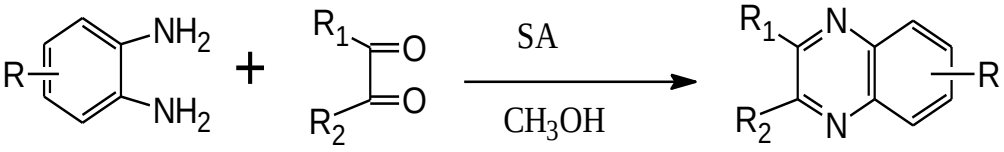
2.1 Iveta Wiedermannova *et.al*, gave scheme for synthesis of some Arylhydrazones of 2-oxo-6, 7 –dichloro- 1, 2-dihydro quinoxaline-3-carbaldehyde showing tuberculostatic activity.[12]



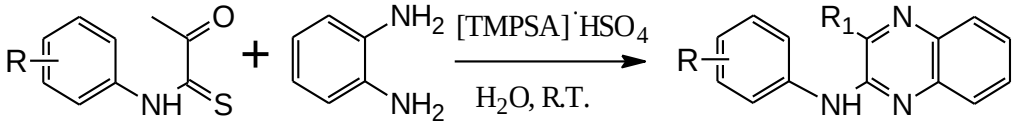
2.2 M. M. Ali *et.al*, synthesized some novel quinoxalinone derivative and evaluated for antimicrobial activity. Condensation of 4-benzoyl-1, 2-phenylenediamine with sodium pyruvate in acetic acid furnished two product which were identified as 6-benzoyl and 7-benzoyl-3-methyl-2(1H) quinoxalinone.[13]



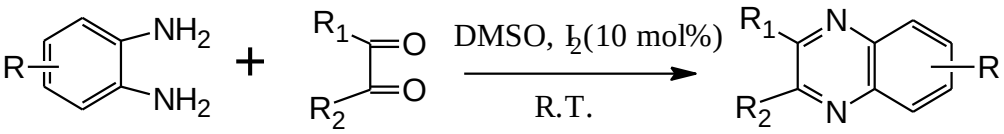
2.3 Hossein Reza Darabi, *et.al*, synthesized a recyclable and highly effective sulfamic acid/MeOH catalytic system for the synthesis of quinoxalines at room temperature. Sulfamic acid/MeOH has been used as an efficient and recyclable catalytic system for the synthesis of quinoxalines. The clean, mild acidity condition, quantitative yields of products, short reaction time and low reaction temperature are attractive features of this reaction which build a suitable method for heat- or acid-sensitive substrates, particularly in drug synthesis.[14]



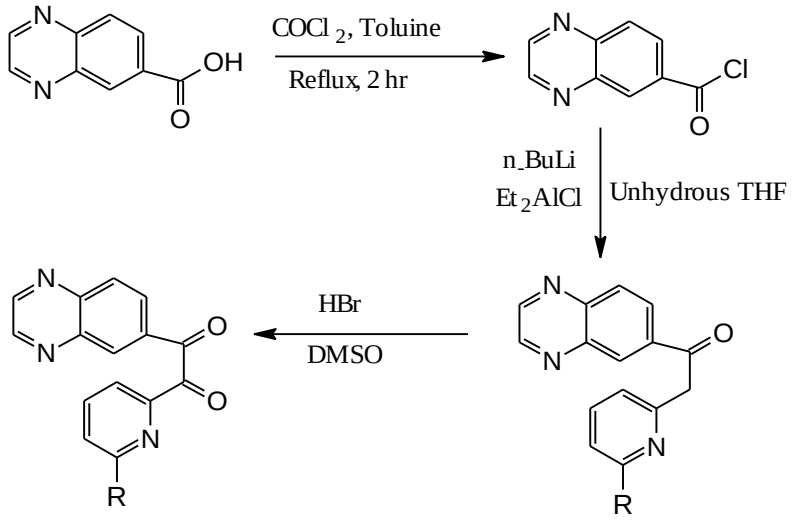
2.4 Fang Dong, Gong Kai, *et.al*, synthesized quinoxaline derivatives catalyzed by task- specific ionic liquid. A cheap and recyclable task-specific ionic liquid N, N, N-trimethyl-N-propanesulfic acid ammonium hydrogen sulphate [TMPSA]·HSO4 was used as the catalyst for the synthesis of quinoxaline derivatives.[15]



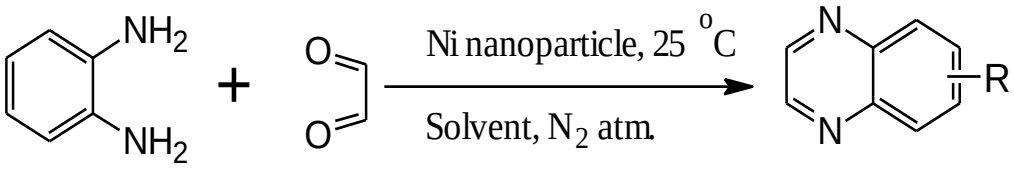
2.5 Rajesh S. Bhosale, Rajendra P. Pawar, *et.al*, synthesized quinoxaline derivatives at room temperature using molecular iodine as the catalyst, The use of molecular iodine as the catalyst for a one-pot synthesis of quinoxaline derivatives at room temperature is reported.[16]



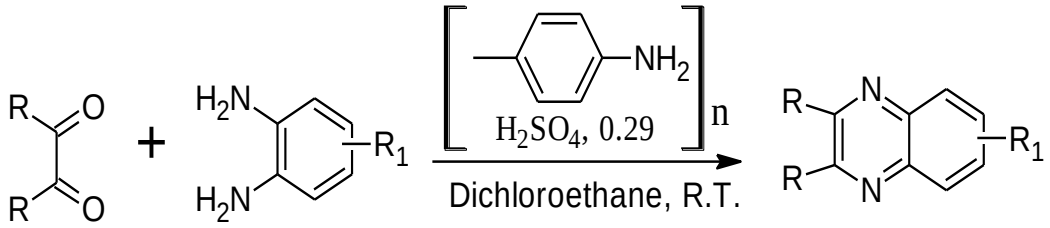
2.6 Dae-Kee Kim *et.al*, reported synthesis of benzenesulfonamide-substituted 4-(6-alkylpyridin-2-yl)-5-(quinoxalin-6-yl) imidazoles.[17]



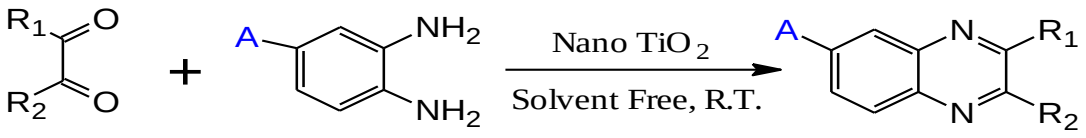
2.7 Ajeet Kumar, Santosh kumar *et.al*, reported the synthesis of quinoxaline using Ni-nanoparticles as a catalyst. In order to elucidate the role of the Ni-nanoparticles, a control reaction was conducted using glyoxal and o-phenylenediamine in acetonitrile in the absence of Ni-nanoparticles. Quinoxaline was formed in around 10 h with a 30% yield. However, the same reaction carried out in acetonitrile using 10 mol% of Ni- nanoparticles (14–18 nm) at 25ºC and stirred under N2 gave quinoxaline in quantitative yield in 10 min.[18]



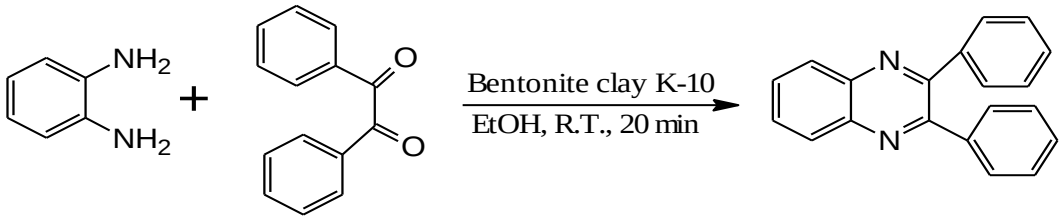
2.8 Chiguru Srinivas *et.al*, gave the scheme for synthesis of quinoxaline derivatives by using polyaniline-sulfate salt catalyst. Biologically important quinoxaline derivatives were prepared in excellent yields using very low amount of reusable polyaniline-sulfate salt catalyst from various 1,2-dicarbonyls and aromatic 1,2-diamines.[19]



2.9 Bi Bi Fatemeh Mirjalili, Ali Akbari *et.al*, reported the synthesis of quinoxaline by using Nano-TiO_2 catalyst. Nano-TiO2 as an eco-friendly and efficient nanocatalyst was applied for quinoxaline preparation with improved yield. In this protocol, diketones and 1,2-diamines were condensed in the presence of catalyst at room temperature.[20]



2.10 Alireza Hasaninejad, Abdolkarim Zare, *et.al*, reported Bentonite Clay K-10 as an Efficient Reagent for the Synthesis of Quinoxaline Derivatives at Room Temperature. Bentonite clay K-10 acts as an efficient reagent for the preparation of quinoxaline derivatives via the condensation of aryl and alkyl 1,2-diamines with α-diketones in ethyl alcohol as a green media at room temperature.[21]



3. AIM AND OBJECTIVES

3.1 Need of study

Quinoxalines are becoming the attractive target of extensive research due to its inherent diverse properties. Various potential activities of the quinoxalines have been explored recently like, antimicrobial agents, cytotoxic agents, anti-tubercular, anxiolytic, anti-HIV, anti-inflammatory, antioxidant etc. In the recent year, 2, 3 Disubstituted quinoxalines reported to posse's significant antimicrobial potential against bacteria, fungi, and mycobacterium (Ganapaty S. *et al* 2007). Design of quinoxaline antibiotics have undertaken by several workers, but they posses limited application due to their toxic effect. According to conclusion derived in literature survey, it was worthwhile to introduced lipophillic moiety into the 2,3 diphenyl quinoxaline system to make the structure as DNA targeted potent antimicrobial agent the sulfonate have created considerable attention as carrier and lipophillic core in the area of synthetic medicinal chemistry. Based on the observation and in connection with earlier studies (Ganapaty *et al*, 2007), the present work was undertaken synthesize some new phenol & aldehyde derivatives of 2, 3 diphenylquinoxaline 7 sulphonyl chloride which are more potential as antibacterial than parent quinoxalines.

3. Aim and Objective

The aim of present study includes:

1. Synthesis and characterization of various phenol & aldehyde derivatives of sulphonyl chloride quinoxaline
2. 1Confirmation of all derivatives
3. Antimicrobial susceptibility testing
4. Determination of MIC
5. Antioxidant screening

   Antioxidants are gaining an importance as a panacea for a large number of life-style diseases like aging, cancer, diabetes, cardiovascular and other degenerative diseases etc. owing to sedentary way of life and stressful existence. Added to these are the deleterious effect of pollution and exposure to harmful chemicals. All the above causes accumulation of harmful free radicals. The role of free radicals is implied and established in various diseases such as aging, cancer, inflammation, rheumatoid arthritis and atherosclerosis Alzheimer's disease. A survey carried out in USA claims that Out of 10 leading causes of death nearly 65% are due to diet related disease, 90% of which occurs due to free radicals. These are heart diseases, cancer, stroke, and diabetes mellitus. To prevail over this situation and secure our body system from free radicals the intake of antioxidant is seems to be supreme.
6. Thus antioxidants act as preventive measure against such life threatening diseases.

4. PLAN OF THE WORK

- Problem Selection
- Literature survey
- Procurement and characterization of raw materials
- Synthesis, purification and characterization of phenol & aldehyde derivatives of sulphonyl chloride quinoxaline
- Antimicrobial susceptibility Testing
- Determination of MIC
- Anti-oxident Screening
- Report.

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